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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,248	05/06/2002	Peter D. Davis	U 013864-1	8432

140 7590 03/09/2005

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,248	DAVIS, PETER D.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/27/04, RCE 10/14/04, and 12/2/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-45* is/are pending in the application.

4a) Of the above claim(s) *10,14 and 37-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-13 and 18-36* is/are rejected.

7)☒ Claim(s) *8 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 and claims 18-45 are currently pending in the instant application. Claims 15-17 were cancelled in the amendment filed 2 January 2004, claims 1-9, 11-13 and 18-36 are rejected and claims 10, 14 and 37-45 are withdrawn from consideration as being for a non-elected subject matter as per the election by original presentation as discussed in the office action of 20 April 2004.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions (the amendment and the 37 CFR 1.132 declaration) filed on 27 August 2004 has been entered. Applicants' amendment in response to the notice of Non-compliant filed 2 December 2004 has also been entered into the application.

Response to Amendment

The declaration under 37 CFR 1.132 filed 27 August 2004 is insufficient to overcome the rejections of claims1-9, 11-13 and 18-36 based upon 35 USC 103(a) as set forth in the last Office action because: the showing is not commensurate in scope to the instant claims and fails to provide unexpected results. Specifically, the instant declaration compares **only one** compound from applicants instantly claimed genus of compounds to one compound from the prior art. Therefore, applicant has not compared

the instantly claimed invention (which comprises many more compounds than have been instantly compared to the prior art) with the closest prior art of record and the showing is not considered commensurate in scope with the instant claims. In re Greenfield, 197 U.S.P.Q. 227 (1978) and In re Lindner, 173 U.S.P.Q. 356 (1972). Also see M.P.E.P. 716.02(d). Furthermore, the statement that the compound of example 2 has antitumor activity shows that the invention works as intended. Specifically, the prior art reference states that the substitution of small alkyl substituents for the 4'-methoxy group of combretastatin A-4 and the loss of the 3'-hydroxyl group does not have a major effect on the interaction with tubulin. Applicant has failed to provide a showing of sufficient scope that applicants' instant compounds have a major effect on the interaction with tubulin as compared to the prior art compound of combretastatin A-4. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Response to Amendment and Arguments

Applicants amendment filed 2 December 2004 has clarified the issue that claim 18 is not canceled and has amended claims 4, 8 and 20 to correct typographical errors. However, the amendment to claim 8 has necessitated the new objection to claims 8 and 28 as being duplicate claims. In regards to the 35 USC 103(a) rejections, applicant's arguments filed 27 August 2004 have been fully considered but they are not persuasive. Applicant argues there is no actual structure taught y the reference wherein the 4'methoxy is replaced and the 3' hydroxyl is maintained and that combretastatin A-4 is the closest prior art structure described and is not sufficiently similar to the claimed

structure to set forth a prima facie case of obviousness. Applicants arguments are not persuasive because while, pages 2 and 3 of the instant specification state that the removal of the 4' methoxy group would considerably reduce the biological activity and that it is unexpected that replacing the 4'methoxy would result in compounds with similar potency, it is noted that Woods et al discloses that the 3' hydroxyl group has a relatively small effect on binding to tubulin and that the 4' methoxy group can be replaced with small hydrophobic groups while still retaining significant activity against tubulin. While there is no formula in the Woods prior art having a hydroxy group at the 3' position (which would be a 102(b) if present) the Woods prior art document does disclose that the 3' OH group is optional and the Woods prior art document does disclose that the cis-methyl and ethyl-stilbenes, wherein the 4' methoxy group has been replaced with methyl or ethyl, does show strong interaction with tubulin and can inhibit assembly of microtubules, cause disruption of intracellular microtubular structure and inhibit colchicines binding to tubulin and are cytotoxic to cultured cells (page 709). Therefore, the 35 USC 103(a) rejections of the claims 1-9 and 11-13 are maintained and newly added claims 18-36 are also rejected.

New Claim Objections

Claim(s) 8 and 28 is/are objected to for being substantial duplicates of one another. Specifically, both claims are claiming the compound (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate. When two claims in an application are duplicates, or else are so close in content that they both cover the same

thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. M.P.E.P. 706.03(k).

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. (reference AT on form 1449).

Applicant's instant claims 1-4 are drawn towards a cis-stilbene of formula (I) (claim 1) wherein R1, R2, R3 can be methyl (claim 2), R5 is hydrogen and R4 is alkyl or halo (claim 3). Claim 4 is drawn to the specific compound (Z) –1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethane.

Determining the scope and contents of the prior art

The prior art reference of Woods et al. discloses Combretastatin A-4, figure 1, page 705, which interacts with tubulin with resultant disruption of microtubular function. Page 709 of Woods et al. discloses that the 4'methoxy and 3'hydroxy groups of

combretastatin A-4 are not essential for the interaction with tubulin. Furthermore, page 710 of Woods et al. discloses Figure 8 which shows that small alkyl groups at a position equivalent to applicant's R4 do not adversely affect activity of the compound and methoxy is not essential at this position. Page 710 discloses that the interaction with tubulin is tolerant of the replacement of the 4'-methoxy by methyl or ethyl, and also, (e) of page 710 discloses that the replacement of the 4'methoxy group of combretastatin A-4 can be replaced with small hydrophobic groups while still retaining significant activity against tubulin

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art reference and the claims at issue is that in the position equivalent to applicant's R4 substituent, the prior art reference contains a methoxy group, which is not a variable included in applicant's instant claims.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art at the time of the invention to prepare compounds of applicant's instant claim 1, which have vascular damaging activity, including compounds of applicants instant claim 1 wherein R1, R2, and R3 are methyl, R4 is alkyl and R5 is hydrogen when faced with combretastatin A4 in the prior art reference of Woods et al. The motivation is provided in the prior art reference by the disclosure that small alkyl groups at the 4' position do not adversely affect activity of the compound, that methoxy is not essential at the 4' position, that the interaction with tubulin is tolerant of the replacement of the 4'methoxy with methyl or ethyl and that the 4'methoxy can be replaced with small hydrophobic groups while still retaining significant activity against

tubulin. The disclosure by Woods et al. that the 4'metoxy group is not necessary and that the replacement of the 4'-methoxy by a small alkyl group or small hydrophobic group would not adversely affect the activity of the compound would motivate someone of ordinary skill in the art to prepare compounds as instantly claimed by applicant in order to have more compounds which are useful for the disruption of microtubular function and for the treatment of tumors.

Claims 5-9, 11-13 and 18-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woods et al. as applied to claims 1-4 above, and further in view of WO 92/16486 or WO 99/35150.

Applicants instant claims 5-9, 11-13 and 18-36 are drawn towards prodrugs of the compound of formula (I), specifically phosphate esters of the compound of formula (I) and compositions of the compound of formula (I)

Determining the scope and contents of the prior art

WO/92/16486 discloses compounds which have greater aqueous solubility than Combretastatin A4 and exhibit greater stability, which are prodrugs such as the compound of formula (I) (page 2) wherein Y is a phosphate or a phosphate derivative, the prodrug of the phosphate derivative is particulary preferred (page 3). These compounds can be dissolved in a phosphate buffered saline (page 20) for the preparation of a pharmaceutical formulation of the compound.

WO 99/35150 discloses combretastatin A4 prodrugs, of which phosphate salts are the most stable and suitable (page 6). Page 7 discloses phosphate ester prodrugs

which are water soluble. These compounds can be added to a sterile vehicle such as water to be administered as a pharmaceutical composition (page 36).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art of WO 92/16486 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

The difference between the prior art of WO 99/35150 and the instant claims is that the prior art reference discloses phosphate ester prodrugs of Combretastatin A-4, wherein the position equivalent to applicant's R4 is a methoxy group and the prior art reference discloses pharmaceutical formulations and their methods of preparation for Combretastatin A-4, wherein position 4' is substituted with a methoxy.

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to someone of ordinary skill in the art to prepare phosphate ester prodrugs of the compound as found in applicants instant claim 1 and to prepare pharmaceutical compositions when faced with the prior art reference of Woods at al. and one of WO 92/16486 or WO 99/35150 since Woods et al. discloses that the 4'methoxy of Combretastatin A-4 can be replaced by a small alkyl group or a small hydrophobic group without causing an adverse reaction in activity and Wo 92/16486 or WO 99/35150 disclose the phosphate ester prodrugs of Combretastatin A4 and disclose that these

phosphate esters have improved aqueous solubility and characteristics for use as a prodrug in pharmaceutical formulations. One of ordinary skill in the art would be motivated to prepare prodrugs of the formula as instantly claimed by applicant and to prepare pharmaceutical compositions by the prior art references to prepare other useful compounds which interact with tubulin and are useful in the treatment of cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier number for accessing the facsimile machine is (571) 272-8300.

KAMAL A. SAEED, PH.D.
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